



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>5</sup> :</b> <b>A61K 9/22, 31/44</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 94/00112</b> <b>(43) International Publication Date:</b> 6 January 1994 (06.01.94)
<b>(21) International Application Number:</b> PCT/SE93/00521 <b>(22) International Filing Date:</b> 11 June 1993 (11.06.93) <b>(30) Priority data:</b> 9201930-6                      24 June 1992 (24.06.92)                      SE <b>(71) Applicant:</b> AKTIEBOLAGET ASTRA [SE/SE]; S-151 85 Södertälje (SE). <b>(72) Inventors:</b> FALK, Karl-Erik, Lennart ; Odönvågen 57, S-437 00 Lindome (SE). SJÖGREN, John, Albert ; Hönekullavågen 47 H, S-435 44 Mönlycke (SE). <b>(74) Agent:</b> LINDEROTH, Margareta; AB Astra, Patent Department, S-151 85 Södertälje (SE).		<b>(81) Designated States:</b> AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> AN ORAL FORMULATION FOR GASTRIC ANTIBACTERIAL TREATMENT AS WELL AS A PROCESS THEREOF AND THE USE  <b>(57) Abstract</b>  An oral formulation with extended release for treatment of infections in the upper gastrointestinal tract as well as processes for the preparation and the use thereof.		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NE	Niger
BE	Belgium	GN	Guinea	NL	Netherlands
BF	Burkina Faso	GR	Greece	NO	Norway
BG	Bulgaria	HU	Hungary	NZ	New Zealand
BJ	Benin	IE	Ireland	PL	Poland
BR	Brazil	IT	Italy	PT	Portugal
BY	Belarus	JP	Japan	RO	Romania
CA	Canada	KP	Democratic People's Republic of Korea	RU	Russian Federation
CF	Central African Republic	KR	Republic of Korea	SD	Sudan
CG	Congo	KZ	Kazakhstan	SE	Sweden
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovak Republic
CM	Cameroon	LU	Luxembourg	SN	Senegal
CN	China	LV	Latvia	TD	Chad
CS	Czechoslovakia	MC	Monaco	TG	Togo
CZ	Czech Republic	MG	Madagascar	UA	Ukraine
DE	Germany	ML	Mali	US	United States of America
DK	Denmark	MN	Mongolia	UZ	Uzbekistan
ES	Spain			VN	Viet Nam
FI	Finland				

AN ORAL FORMULATION FOR GASTRIC ANTIBACTERIAL  
TREATMENT AS WELL AS A PROCESS THEREOF AND THE  
USE

5    Technical field

The invention relates to formulations for treatment of infections in the upper gastrointestinal tract especially infections caused by *Helicobacter pylori*, and a process for the manufacture of said formulations as well as the use thereof.

10

Said formulations give a prolonged release of antimicrobial agent(s) in the upper gastrointestinal tract.

Background of the invention

15    *Helicobacter pylori* (*H.pylori*) is a recently discovered bacterium, cultured for the first time in Australia 1982 [Warren JR Lancet 1983;1:1273], which has attracted much interest due to its possible aetiological role in a number of disorders in the upper gastrointestinal tract. It is considered a major cause in the  
20    development of peptic ulcer disease [*Helicobacter pylori* Working Party Report. World Congress in Gastroenterology, Sydney 1990] *H. pylori* is accepted as the aetiological agent in most cases of chronic non-specific gastritis. Chronic active gastritis is highly correlated to *H. pylori*-infections. The organism is found in  
25    association with chronic active gastritis in almost 100% of the cases. Further, it was concluded in a case-control study of 372 patients that infection with *H. pylori* is associated with an increased risk of gastric adenocarcinoma and may be a cofactor in the pathogenesis of this malignant condition [Parsonnet J,  
30    Friedman GD, Daniel MS et al. N Engl J Med 1991;325:1127-31].

The pathogenic mechanism of *H. pylori* is not yet known in its

details. The mode of transmission is unknown but considered to be by the faecal oral route and may be waterborne. *H. pylori* is found throughout the world but there is a higher prevalence of the organism in less developed countries and in patients with low economic status in western countries. The overall prevalence in western countries is about 52 % and increases with advancing age.

*H. pylori* is a Gram-negative microaerophilic bacterium which is about 3.5  $\mu\text{m}$  in length and 1  $\mu\text{m}$  in diameter. Due to the presence of 4-6 flagella attached to the end of its typical S- or spiral shape form, the bacterium can move rapidly in mucus. It lives closely attached to the gastric epithelial cells beneath the mucus layer and colonises the stomach, mainly the antrum, in a patchy fashion.

In vitro studies show a high sensitivity of *H. pylori* to many antibiotics [McNulty CA, Dent JC. Eur J Clin Microbiol Infect Dis 1988;7:566-569], [Lambert T, Megraud F, Gerbaud G et al. Antimicrob Agents Chemother 1986;30:510-511]. However, in vivo studies have demonstrated that there is a small correlation between in vitro sensitivity for *H. pylori* and treatment results in vivo for antibacterial drugs. The eradication regime with best eradication results today (elimination of *H. pylori* in 80-90% of treated patients) is triple therapy [Axon ATR. Scand J Gastroenterol 1989;24(suppl 160) :35-38.]. The therapy is a combination of a bismuth preparation, metronidazole and amoxicillin or tetracycline. However, the dosage regimen involves many tablets and there is a need of administration several times per day. This is difficult for the patient to follow and compliance has been shown to be important to achieve the high eradication

rates. Adverse effects, mainly due to metronidazole or bismuth are very common. About 30% of the patients have reported side effects [Axon ATR, Scand J Gastroenterol 1989;24(suppl 160):35-38].

5

Monotherapy of different antibiotics which are known to have good effect in vitro against *H.pylori* is insufficiently effective in vivo. Amoxicillin, for example, eradicates *H.pylori* only in about 20% of treated patients. Combination of two drugs give higher eradication rates than monotherapy. Bismuth preparations (bismuth subsalicylate or colloidal bismuth subcitrate) in combination with amoxicillin eradicated *H.pylori* in 44 % of treated patients, bismuth + metronidazole, amoxicillin + tinidazole and amoxicillin + metronidazole in about 55 % of the patients, respectively [Chiba N, Rademaker JW, Rao BV et al. Gut 1991;32:A1220-1221 Abstract].

10

15

Antibacterial agents have also been combined with acid secretion inhibitors. Combinations with histamin<sub>2</sub>-blockers show no improved effect. Proton pump inhibitors e g omeprazole, which have very little anti-*H.pylori* effect on its own show a synergistic effect in combination with antibiotics. A dose of 750 mg amoxicillin twice daily with 40 mg omeprazole once daily was reported to eradicate *H.pylori* in 54% of the patients [Unge P, Eriksson K, Bergman B. et al. Gastroenterol 1992;102(4);A183(abstract)]. Any explanation for this synergistic effect is not yet known, according to available information.

20

25

Many antibiotics have relatively short duration of action and are given 3-4 times a day. Attempts to prolong the action by use of prolonged release products have generally been unsuccessful

30

because the absorption of the antibiotic from the gastrointestinal tract is poor when administered in slow release form [Delgado Charro MB, Vila Jato JL. Int J Pharm 1992;78;35-41] Instead antibiotics are given in rapidly absorbed formulations, e g tablets or capsules. In order to achieve sufficiently long duration of action higher doses are given.

In all previous studies on H.pylori eradication rapidly available dosage forms of the antibacterial agents have been used and attempts have been made to increase the success rate by using very high doses of antibacterials as well as proton pump inhibitors. For example, 82% of treated patients were eradicated after 10 days therapy of 40 mg omeprazole twice daily in combination with 1 g amoxicillin twice daily followed by 6 weeks monotherapy of 20 mg omeprazole once daily.[Bayerdörffer E, Mannes GA, Sommer A et al. Gastroenterol 1992;102(4):A38(abstract)].

#### Outline of the invention

We have discovered that the effectiveness of the treatment can be improved in an entirely different way, namely by administration of the antibacterial agents in prolonged release formulations and administer the formulations in such a way that they stay in the stomach several hours. It is not yet known if the H.pylori bacterias are accessible for treatment by antibacterial agents in the stomach or if the drug has to be absorbed and reach the bacterias via the blood circulation. The improved effect of formulations according to this invention may indicate that a local effect in the stomach is important.

30

Examples of formulations with prolonged gastric residence time

are bioadhesive systems which interact with mucus or the mucosa. Another way to prolong the residence time is swelling systems which expand in contact with the gastric fluid to a size which does not allow the system to pass through the pylorus.

5 Further examples are formulations with very high density or systems which float on the gastric contents. It has also been observed that large non-disintegrating tablets or capsules can be retained for several hours in the stomach. The retention time in the stomach is especially prolonged when the tablet or capsule is  
10 administered together with food due to the sieving function of pylorus when the stomach is in the digestive mode [Davis SS, Hardy JG, Taylor MJ et al. Int J Pharm 1984;21:331-340]. Food also retards the emptying of tablets or pellets, but the effect is less pronounced. The critical size is reported to be about 7 mm  
15 [Khosla R. Nottingham: University of Nottingham, 1987.(Diss).]

The drug should be released within 1-24 h, preferably 1-6 h. To achieve an effective treatment of H.pylori infection the product should remain in the stomach at least 2-4 h, preferably more than  
20 6 h. The major part of the drug should be released before the tablet leaves the stomach. The drugs suitable for the preparations according to the invention are e.g. ampicillin, amoxicillin, benzylpenicillin , phenoxymethylpenicillin, bacampicillin, pivampicillin, carbenicillin, cloxacillin, cyclacillin, dicloxacillin,  
25 methicillin, oxacillin, piperacillin, ticarcillin, flucloxacillin, cefuroxime, cefetamet, cefetrame, cefixime, cefoxitin, ceftazidime, ceftizoxime, latamoxef, cefoperazone, ceftriaxone, cefsulodin, cefotaxime, cephalixin, cefaclor, cefadroxil, cefalothin, cefazolin, cefpodoxime, ceftibuten, aztreonam, tigemonam, erythromycin,  
30 dirithromycin, roxithromycin, azithromycin, clarithromycin, clindamycin, paldimycin, lincomycin, vancomycin, spectinomycin,

tobramycin, paromomycin, metronidazole, tinidazole, ornidazole, amifloxacin, cinoxacin, ciprofloxacin, difloxacin, enoxacin, fleroxacin, norfloxacin, ofloxacin, temafloxacin, doxycycline, minocycline, tetracycline, chlortetracycline, oxytetracycline, 5 methacycline, rolitetracyclin, nitrofurantoin, nalidixic acid, gentamicin, rifampicin, amikacin, netilmicin, imipenem, cilastatin, chloramphenicol, furazolidone, nifuroxazide, sulfadiazin, sulfametoazol, bismuth subsalicylate, colloidal bismuth subcitrate, gramicidin, mecillinam, cloxiquine, 10 chlorhexidine, dichlorobenzylalcohol, methyl-2-pentylphenol. The active agents could be in standard forms or used as salts, hydrates, esters etc. A combination of two or more of the above listed drugs may be preferable, for example to minimize the risk for developing resistance. The antimicrobial agents can also be 15 combined with other drugs used in the treatment of acid related diseases e.g. acid pump inhibitors or H<sub>2</sub>-blockers, such as for example omeprazole.

Possible formulations to be used are large non-disintegrating 20 tablets or capsules e.g. inert matrix tablets [Hui H, Robinson JR, Lee VHL. Design and fabrication of Oral Controlled Delivery Systems. In: Robinson JR, Lee VHL, eds. Controlled Drug Delivery. Fundamentals and applications. New York: Marcel Dekker, Inc, 1987:373-432], osmotic pumps [Davis SS, Fara JW. 25 Osmotic pumps. In: Hardy JG, Davis SS, Wilson CG, eds. Drug Delivery to the Gastrointestinal Tract. Chichester: Ellis Horwood Limited, 1989:97-109.] and membrane-coated tablets. Further, swelling systems [Banker, US Patent + no 261,242,] floating systems [Davis SS, Stockwell AF, Taylor MJ et al. Pharm Res 30 1986;3:208-213.], [Washington N, Wilson CG, Greaves JL et al. Scand J Gastroenterol 1988;23:920-924], formulations with high



density [Devereux JE, Newton JM, Short MB. J Pharm Pharmacol 1990;42:500-501] and mucoadhesive systems [Junginger HE. Pharm Ind 1991;53:1056-1065] prepared from e.g. polycarbophil, polyacrylic acid, methylcellulose, polyethylene oxide, chitosan, tragacanth, sodium carboxymethyl cellulose can be used.

An example from the above listed formulations is the inert porous matrix tablet which is obtained by mixing the drug with waxes or water insoluble polymers and with fillers and binders. Paraffin, polyvinylchloride, ethylcellulose, stearyl alcohol, cetyl alcohol, carnauba wax, polyethylene, polyvinyl acetate, polymethyl methacrylate could be used as suitable diffusion retarding compounds. Other excipients used in the preparations of such tablets are e.g. lactose, mannitol, calcium phosphates, magnesium stearate, hydroxypropyl methylcellulose, methylcellulose, polyvinylpyrrolidone, aluminium silicate, sodium carbonate, potassium phosphate or other suitable materials.

Examples

It is the object of the present invention to provide an extended-release preparation with prolonged gastric residence time after oral administration, containing one or more antimicrobial agents.

5

## Example 1:

g

	Amoxicillin sodium	830
	Paraffin	500
10	Ethylcellulose	60
	Magnesium stearate	28.8

Amoxicillin sodium was mixed in a planetary mixer for 5 minutes with paraffin. The resultant mixture was then moistened for 5 minutes with a solution of ethylcellulose in isopropanol and dried. The granulate was milled through a 1.0 mm sieve and lubricated for 2 minutes with magnesium stearate.

The granulate was compressed to tablets on a tableting machine fitted with 13 mm punches. Each tablet contained 415 mg amoxicillin sodium. The release profile of the drug is shown in Figure 1.

## Example 2:

g

25

	Amoxicillin trihydrate	215.6
	Paraffin	250
	Sodium carbonate	209
	Ethylcellulose	30
30	Magnesium stearate	14.1

The composition according to Example 2 was formed to modified release tablets containing 375 mg of amoxicillin/tablet. The tablet were prepared in the following way:

- 5 Amoxicillin trihydrate, paraffin and sodium carbonate were mixed for 5 minutes in a planetary mixer. The remaining process was made according to Example 1. The release profile of the drug is shown in Figure 2.

10	Example 3	g
	Amoxicillin trihydrate	215
	Tripotassium phosphate	209
	Polyvinylpyrrolidone	20
15	Magnesium stearate	20

- Compressed into tablets after granulation and drying as in Example 1. The tablets were coated with a porous membrane coating consisting of polyvinyl chloride in acetone according to
- 20 [Källstrand G, Ekman B. J Pharm Sci 1983;72(7):772-775].
- Micronized sucrose (particle size less than 10  $\mu\text{m}$ ) was suspended in the polymer solution. Coating was achieved by spraying the suspension on a moving bed of tablets with an airless sprayer. Coating was continued until the weight of the coat on each tablet
- 25 was 50 mg.

## Example 4:

g

	Amoxicillin trihydrate	244
	Ethylcellulose	268
5	Chitosan	366
	Hydrochloric acid	0,13
	Water purified*	q.s.
	Ethanol*	q.s.

- 10 \*Used in the manufacture of pellets but removed during subsequent processing

The bioadhesive pellets were manufactured using conventional fluid-bed coating technology. Amoxicillin trihydrate was  
15 successively coated with solutions containing chitosan and ethylcellulose, respectively.

Claims

1. An oral formulation containing active materials for treatment of infections in the upper gastrointestinal tract characterized in  
5 that the formulation is retained in the stomach for a prolonged time whereby the active materials are released continuously during said time.
2. A formulation according to claim 1 where the preferred  
10 retention time is at least 1 h during which period the active materials are released continuously.
3. A formulation according to claim 1, wherein the formulation contains one or more antibacterial agents.  
15
4. A formulation according to claim 1 where the infection is caused by *Helicobacter pylori*.
5. A formulation according to claim 1 wherein the active  
20 substance is amoxicillin.
6. A formulation according to claim 1 comprising a combination of two or more active agents.
- 25 7. A formulation according to claim 1 where the dosage form has bioadhesive properties.
8. A formulation according to claim 1 consisting of a non-disintegrating prolonged release formulation containing  
30 antibacterial agents.

9. A formulation according to claim 8 wherein the size is not less than 7 mm.
10. A formulation according to claim 9 where the release of the  
5 active compound is controlled by a non-disintegrating membrane.
11. A formulation according to claim 9 where the formulation is an inert porous matrix.
- 10 12. A process for the manufacture of a preparation according to claim 11 wherein the active substance is mixed with polymers or materials in an amount exceeding 10% of the weight of the mixture and the resulting mixture is compressed into a tablet.
- 15 13. A process according to claim 12 wherein the tablet is heated to a temperature above the melting point of the waxy material to retard the release profile and improve the mechanical strength of the tablet.
- 20 14. Use of a formulation according to claim 1 in the preparation of an active dosage form for the treatment of infections in the upper gastrointestinal tract.
15. Use of a formulation according to claim 1 together with acid  
25 secretion inhibitors.
16. Use of a formulation according to claim 1 together with proton pump inhibitors.
- 30 17. Use according to claim 16 wherein the proton pump inhibitor is omeprazole.

1/1

EXAMPLE 1 PHOSPHATE BUFFER, pH 4.5, 100 rpm

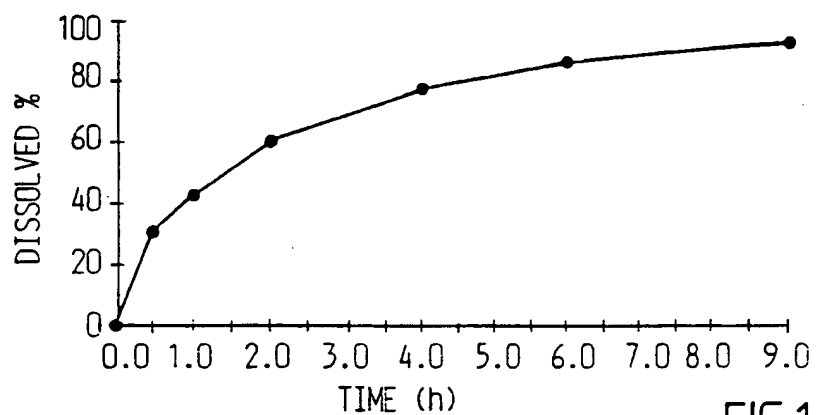


FIG.1

EXAMPLE 2 PHOSPHATE BUFFER, pH 4.5, 100 rpm

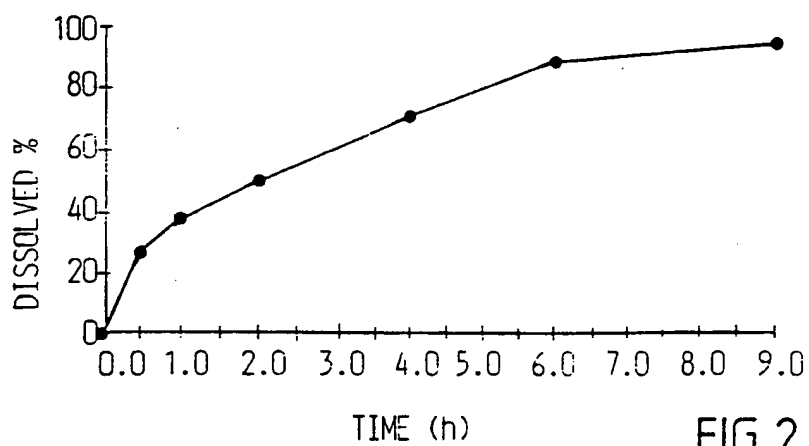


FIG.2

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 93/00521

## A. CLASSIFICATION OF SUBJECT MATTER

IPC5: A61K 9/22, A61K 31/44

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC5: A61K, C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, WPIL, CLAIMS, EMBASE, MEDLINE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP, A1, 0490450 (BROCADES PHARMA B.V.), 17 June 1992 (17.06.92), see page 2, line 1 - line 47; page 7, line 40 - line 49; example 5; claims 11-15 --	1-6, 14-17
X	WO, A1, 9119486 (KALMO ENTERPRICES, INC.), 26 December 1991 (26.12.91), see page 9, line 4 - page 10, line 17; claims 1-6 --	1-8
X	EP, A2, 0455475 (RECKITT AND COLMAN PRODUCTS LIMITED), 6 November 1991 (06.11.91), see page 2 - page 3, line 47, claims --	1-4, 7-14

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

## \* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

27 Sept 1993

Date of mailing of the international search report

29 -09- 1993

Name and mailing address of the ISA/  
Swedish Patent Office  
Box 5055, S-102 42 STOCKHOLM  
Facsimile No. +46 8 666 02 86

Authorized officer

Anneli Jönsson

Telephone No. +46 8 782 25 00



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 93/00521

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>Current Opinion in Gastroenterology, Volume 8, 1992, C.S. Goodwin et al, "Peptic ulcer disease and Helicobacter pylori infection" page 122 - page 127</p> <p style="text-align: center;">--</p>	1-17
E,A	<p>Dialog Information Services, file 154, MEDLINE, Dilaog accession no. 08302546, MEDLINE accession no. 93012546, Rune S: "Helicobacter pylori, peptic ulcer disease and inhibition of gastric acid secretion", Digestion (SWITZERLAND) 1992, 51 Suppl 1 p11-6</p> <p style="text-align: center;">-- -----</p>	1-17

**INTERNATIONAL SEARCH REPORT**  
Information on patent family members

26/08/93

International application No.  
PCT/SE 93/00521

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
EP-A1-	0490450	17/06/92	AU-A-	9134791	08/07/92
			WO-A-	9210502	25/06/92
-----					
WO-A1-	9119486	26/12/91	AU-A-	8219191	07/01/92
-----					
EP-A2-	0455475	06/11/91	AU-A-	7596891	07/11/91
			GB-A-	2243549	06/11/91
-----					

**This Page is Inserted by IFW Indexing and Scanning  
Operations and is not part of the Official Record**

**BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☒ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** \_\_\_\_\_

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.**